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LEUKEMIA

A Review of 65 Cases

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Leukemia has been described repeatedly in case reports since the early days of recorded medical history. It was not recognized as an entity until 1845 when Virchow first used the term leukemia and interpreted the disease or "an excessive formation of white blood cells." Although the etiology is unknown, the most widely accepted hypothesis is that leukemia is a malignant neoplasm involving only one type of blood cell in each instance. Heredity and chronic irritation are thought to be predisposing factors. The disease has occurred in parent and child, in siblings, and in identical twins somewhat more often than can be accounted for by chance but the inherited predisposition seems slight. There is a much greater incidence of leukemia in individuals who are exposed for long periods to alpha, gamma, or x-rays. Prolonged subjection of humans or animals to benzol has produced leukemia. Burns and other forms of trauma have been suspected of being etiologic agents in some cases but this has not been confirmed statistically. Malaria, tuberculosis and many acute infections have been cited as precipitating factors but this too is unconfirmed. Leukemia in mice, which is similar to that in man, has been transmitted from animal to animal by transfusing leukemic cells. Cell free filtrates did not transmit the disease. Similar experiments with human donors and recipients have failed. Leukemia in fowls, which is dissimilar to that in man, can be transmitted by cell free filtrates. Intensive investigation has not substantiated an infectious, endocrinological, or metabolic etiologic factor. Since the incidence of leukemia has increased in recent years some writers have suggested that the sulfonamides may be causally related. However, this apparent increase in incidence may be due to a more frequent recognition of the aleukemic form of the disease.

Leukemia occurs infrequently in the newborn infant but acute leukemia (with a duration not exceeding six months) has its greatest incidence in the first five years of life. In this age group the disease usually ends fatally in a few weeks or months. In older children subacute leukemia (with a duration of from six months to a year) occurs infrequently, and chronic leukemia (with a duration exceeding a year) is rare.

The three most common cytological types are the myeloid, lymphoid, and monocytic. Eosinophilic leukemia is extremely rare and basophilic leukemia and megakaryocytic leukemia are thought to be not true entities

but merely atypical myeloid leukemias. Formerly it was thought that the great majority of the leukemias in childhood were lymphoid. This has been shown to have been due to mistaking micromyeloblasts for lymphocytes. It is now known that lymphoid leukemia is not much, if any, more frequent than myeloid leukemia in children. Monocytic leukemia is uncommon. In many cases the predominating cell is the blast

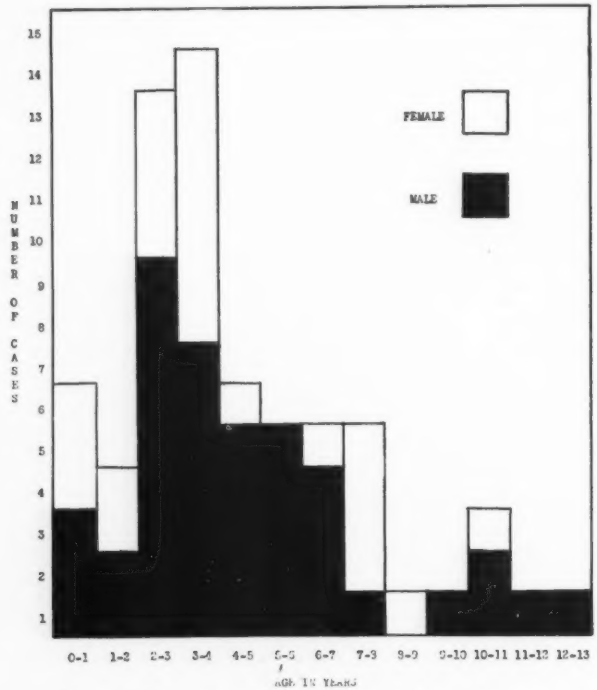

CHART I. Leukemia (65 cases), sex and age incidence

form (either myeloblast, lymphoblast, or monoblast) and unless there are an appreciable number of large cells present which can be shown by the use of the peroxidase stain to be either promyelocytes or prolymphocytes, no cytological diagnosis can be made. Since young monocytic forms may be either peroxidase positive or negative, the problem is further complicated. Supravital preparations may show the characteristic cell movement and cytoplasmic staining of each type and examination of infiltrating cells in biopsy or autopsy tissue are of value in identifying a monoblastic leukemia.

Unless all of these methods have been exhausted it is preferable not to use the term stem cell leukemia but to designate a doubtful type as undifferentiated leukemia.

However, the cytological diagnosis is of academic interest only since the clinical course is similar in all types. There is a tendency for lymphoid leukemia to have more marked lymphadenopathy. The splenomegaly is greater in subacute and chronic myeloid leukemia. Swelling and ulceration of the buccal mucosa is more constantly found in monocytic leukemia.

From 1938 through 1947 sixty-five cases of leukemia were seen at the Children's Hospital. Their ages ranged from two months to twelve years and 48 of the cases (73.8%) occurred in the first six years of life (see Chart I). As in Wintrobe's series of 50 acute leukemias there was a predilection for white patients. Fifty-six were white and only 9 were colored. Since the incidence of white to colored admissions in this hospital is about 2.2 to 1 the comparative incidence of leukemia in white and colored patients when corrected for this admission rate is about 2.8 white to 1 colored patient. All published series of leukemia in children show the disease to be twice as prevalent in males as in females. In Cooke's series of 50 cases, 64.0% were males. In this series 41 were male giving an incidence of 73.1% (see Chart I).

Lambin and Gerard found that in 54 cases of acute leukemia 17 cases occurred during the months from May to October, while 37 cases had their onset in the winter months. Of the 65 cases reported here, 39 began during the summer months and only 26 began during the winter months. The cases that we have classified as subacute or chronic were equally divided in their time of onset between the summer and winter months.

The Month of Onset (65 cases)

May	6	
June	6	
July	6	39 cases (Summer)
August	11	
September	6	
October	4	
November	5	
December	11	
January	3	26 cases (Winter)
February	2	
March	2	
April	3	
Total	65	

The most common chief manifestations were pallor, listlessness, irrita-

bility, anorexia, weight loss, and fever. Some combination of these complaints were present in 21 cases. Infection was the main disturbance in 12 instances. There were 11 upper respiratory infections and one infected tooth. Bone or joint pain was the outstanding symptom in 11 cases. Cutaneous petechiae or ecchymoses were the presenting complaints in 6 cases. Enlarged lymph nodes or an enlarged spleen were the most prominent signs in 5 cases. Abdominal pain was the chief complaint in 4 cases, bleeding (1 hemoptysis, 1 tooth socket, 1 melena) in 3 cases, stupor in 2 cases and vomiting in 1 case.

Chief Manifestations

Pallor and asthenia	21
Infection	12
Limb symptoms	11
Skin petechiae or ecchymoses	6
Enlarged lymph nodes or spleen	5
Abdominal pain	4
Bleeding	3
Stupor	2
Vomiting	1
Total	65*

* Cases.

As in other series, infections preceded or accompanied the signs of the disease in a sizeable proportion of our group (29 cases or 44.6%). There were 25 upper respiratory infections ("colds", tonsillitis or pharyngitis, sinusitis, flu, otitis media). There was one case each preceded by scarlet fever, pneumonia, pleurisy, and an abscessed tooth. The high incidence of associated acute infections does suggest that they may be a precipitating factor, but, as Osgood points out, the infections may be a result of lowered resistance due to the paucity of mature neutrophiles.

Onset Preceded or Accompanied by Acute Infection 29 cases (44.6% of series)

Upper respiratory infection		25
Tonsillitis or pharyngitis	13	
"Cold"	7	
Sinusitis	2	
Flu	2	
Otitis media	1	
Abscessed tooth		1
Pneumonia		1
Pleurisy		1
Scarlet fever		1
Total		29

There was a history of sulfonamide medication prior to hospitalization in 20 cases. In 11 of these characteristic signs of leukemia preceded the use of the sulfonamide. In 4 cases agranulocytosis or aplastic anemia due to sulfonamide therapy was suspected. The sequence of events was that a child would develop signs of an upper respiratory infection for which he would be given a sulfonamide. Because of pallor a blood examination would be done revealing anemia, leukopenia and agranulocytosis. The technician would not recognize abnormal cells if they were present and the thrombocytopenia would be known of only when a thrombocyte count was requested. There is no evidence in this series that sulfonamides are causally related to leukemia.

Twenty-one (32.3%) of the children in this group had symptoms related to bones or joints when admitted to the hospital. In six cases the involved joints were swollen but in only one were the joints red and in none was local heat increase mentioned. The joint pains in some cases were migratory and simulated those of rheumatic fever. Two cases of pseudoparalysis apparently due to pain suggested poliomyelitis, hysteria, or progressive muscular dystrophy (atrophy of the lower limb musculature was described in one case). One case of true hemiparesis was found to be due to an intracranial hemorrhage. One case had lower limb pain with x-ray changes which were interpreted as osteomyelitis for six weeks until the blood picture was characteristic of leukemia. Positive x-ray findings in the bones were found in only seven cases but x-ray examination was not routinely done. Bone pain in those cases which show no x-ray evidence of pathology is thought to be due to an increase in intra-osseous pressure caused by the rapidly proliferating marrow cells. Except in fulminating acute leukemia bone changes demonstrated by x-ray examination will usually make their appearance. The characteristic film shows evidence of a spotty, generalized production and destruction of bone with areas of decreased density near the metaphyses of the long bones. There may be periosteal elevation with new bone formation. Areas of rarefaction in the skull cannot be differentiated from osteomyelitis or neoplastic metastases. The generalized changes may resemble those found in hyperparathyroidism (Figs. I and II).

In reviewing records, the findings of hepatosplenomegaly and lymphadenopathy are always hard to evaluate. However, the liver was definitely not enlarged in 21 cases (32.3%) on admission nor was the spleen palpable in 17 cases (26.2%). There was no significant lymphadenopathy in 12 cases, 18.5%.

Twenty-one children (32.3%) were described as being "yellow" or "lemon yellow" on admission. Their sclerae were not icteric. This group was slightly more anemic than the rest of the series. The yellow color deep-

ened to such an extent during the course of some that it would seem that intracutaneous oozing hemorrhage with the deposition of blood pigment may account for some of this color change.

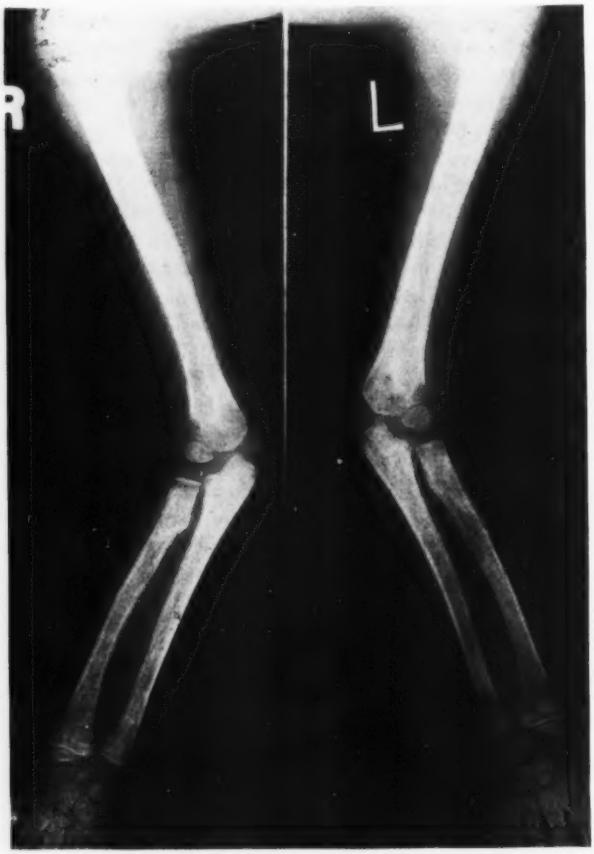

FIG. I. Note leukemic infiltrations of the Medullary regions particularly in the distal portions of the radius and ulna. There is also some periosteal reaction in the right humerus.

A systolic, apical, soft or slightly harsh heart murmur was discovered in 28 patients (43.1%). It was usually easy to classify these murmurs as functional (or hemic) but in the presence of joint pains rheumatic carditis

was suggested and when petechiae were present, bacterial endocarditis was simulated.

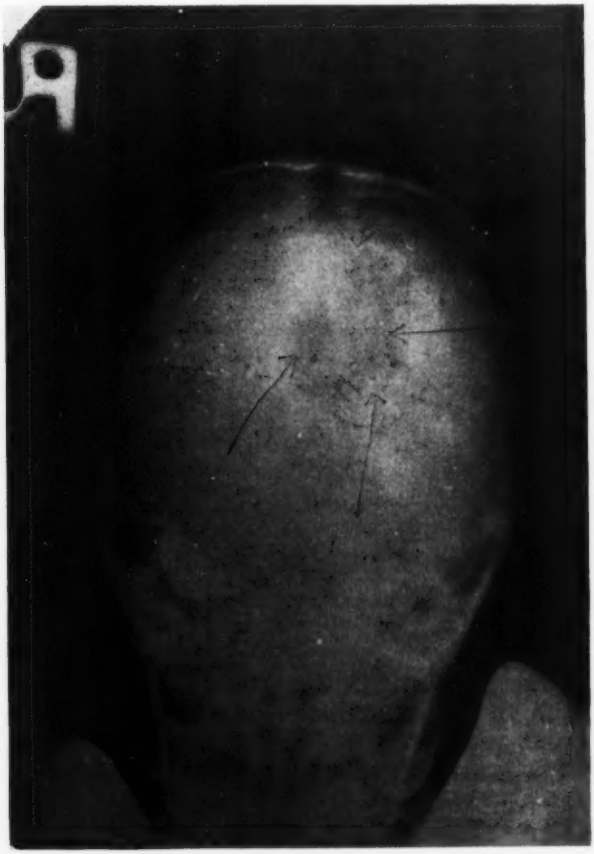

FIG. II. X-ray of the skull, which does not re-produce too well, showing darkened areas of decreased density due to proliferative cellular changes in the inter-osseous space. This finding is not uncommon in leukemia.

Bleeding manifestations either in the immediate history or found on the physical examination were present in 44 cases (67.7%). They are tabulated below:

Bleeding Manifestations on Admission 44 cases = 67.7%

Skin petechiae or ecchymoses	35
Mucous membrane petechiae or bleeding	9
Traumatic bleeding excessive	2
Melena	2
Blood in spinal fluid	2
Hempotysis	1

The bleeding tendency in leukemia is due to thrombocytopenia which results from the pressure destruction by the leukemic cells of all other cellular elements in the bone marrow. This accounts for the anemia as well as for the usual paucity of cell types other than that of the leukemic cell in the peripheral blood. The red blood cell count on admission in this series ranged from 0.57 to 4.26 million (average—2.40 million). Only thirteen patients had red blood counts that exceeded 3 million. The anemia in leukemia is usually described as being normocytic and normochromic. Although volume and color indices were not done on our patients, microcytosis and hypochromia were common. Appreciable numbers of normoblasts were often seen in the peripheral blood smears, sometimes constituting 10% or more of the nucleated cells.

Aleukemic leukemia implies that no immature white blood cells are seen in the peripheral blood. However, most hematologists use this term as synonymous with subleukemic leukemia, indicating those cases in which the white blood count is not elevated. In this series the white blood count on admission ranged from 600 to 454,000. One case died before a white count could be done. In the remaining 64 cases, 33 (51.5%) had white blood counts under 12,000 on admission and 41 (64.0%) never had counts over 20,000 during the entire hospital course. Only 36% of this series was frankly leucocytic leukemia. The thrombocyte count on admission varied from less than 5,000 to 150,000. In only 8 cases was the thrombocyte count over 50,000 on admission. In this series there were 34 undifferentiated leukemias, 21 lymphoid, 9 myeloid, and 1 monocytic leukemia.

Bone marrow aspirations were done in 23 cases. Four or five drops of blood were aspirated from the sternal or tibial marrow and smears were made directly and stained with Leishman's and the peroxidase stains. Usually the predominating cell present was the blast form often accounting for more than 90% of the white cell series rather than the expected 2%. In a few cases the presence of a sizeable percentage of peroxidase positive cells indicated a myeloid leukemia. Platelets and megakaryocytes were absent or greatly diminished. There was invariably a marked depression of erythropoiesis as evidenced by a decrease in the number of nucleated red blood cells so that the proportion of white cells to nucleated red cells was far above the expected, 7-4 to 1. Although this method of bone mar-

row examination is usually satisfactory, in a few instances the results were inconclusive or misleading apparently due to dilution of the specimen with peripheral blood. In the procedure now employed, the direct smears are made, 2 cubic centimeters of marrow fluid are centrifuged and smears are made from the white cell layer, and finally marrow particles are separated from the red cell layer, fixed in formalin, and sectioned as for tissue examination.

Red Blood Cell Count (63 cases)

Range—0.57 to 4.26 million
Average—2.40 million
Over 3.0 million—13 cases

White Blood Cell Count (64 cases) (on admission)

Range—600 to 454,000
Under 12,000—33 cases (52%)
Subleukemic (aleukemic) leukemias—64%
Leukocytic leukemias—36%

Thrombocyte Count (61 cases) (on admission)

Range—5,000 to 150,000
Average—20,000
Number over 50,000—8 cases

Cytological Diagnosis (65 cases) (on admission)

Undifferentiated leukemia	34
Lymphatic leukemia	21
Myeloid leukemia	9
Monocytic leukemia	1
Total	65

Occasionally in the course of lymphatic leukemia large tumor nodules will develop in the viscera, skin, or in the lymph nodes of the superior mediastinum. During the course of lymphosarcoma the characteristic findings of lymphatic leukemia may appear in the peripheral blood and in the bone marrow. The term leukosarcoma designates this group of which there were three in our series. One had a large mediastinal tumor which caused coughing and dyspnea, one had nodules in the liver, and one had nodules in the kidney. Chloroma is a rare variation of myeloid leukemia characterized by local deposits of gray-green tumor tissue in the retro-orbital space, on the periosteum of the flat bones and elsewhere. Only one such case has been seen at the Children's Hospital in the past ten years but since it was seen only in the out patient department it was not included in this series.

Leukemia of the skin was foun in only two cases at this hospital. In one the lesions appeared first on the cheeks and spread to the forehead and

later to the forearms. They were erythematous and maculopapular and some were nodular. They had been present for one month when the child was admitted. In the other case multiple bluish nodules measuring 1 centimeter in diameter appeared on the scalp and ankles in the course of 3 to 4 days.

The treatment of acute leukemia in children is merely palliative. Blood transfusion is the only measure that prolongs life appreciably and no recoveries have been authenticated. Except in the rare cases of chronic leukemia it is questionable whether repeated transfusions are desirable since little comfort or extension of life is afforded and the end is inevitable. However, the decision concerning the continuation of blood transfusions is usually left to the parents. In the cases reviewed here pentnucleotide, folic acid and liver extract were employed in a few instances and had no appreciable effect. X-ray therapy was used in nine cases. When there is disability due to enlarged lymph nodes or an enlarged spleen or localized leukemic growths, x-ray therapy is valuable. There is a reduction in the white count and the thrombocyte and red cell precursors may be similarly destroyed so that the cases suitable for x-ray therapy are limited. Other agents employed in a few of our cases were Fowler's solution, ethyl urethane, colchicine, Staphylococcus toxoid and immunogen, and copper, nickel and zinc organic compounds. Although these agents have transient effects on various hematological components and some of them will reduce leukemic enlargements, none of them have been clinically useful in acute leukemia. Radioactive phosphorus has not been used at this hospital. It is reported to be of value in the management of chronic forms of leukemia but useless or deleterious in acute forms since it may cause more leukopenia, thrombocytopenia and anemia.

The most promising agents under investigation are the folic acid antagonists, particularly aminopterin (4-aminopteroyl-glutamic acid). Farber and Diamond and their co-workers have reported striking remissions in 10 out of 16 patients treated with this substance. The clinical response and the return of the peripheral blood and bone marrow to normal were remarkable. At the time of their report the remissions were of three months' duration.

Autopsies were done on 21 patients. The most constant gross findings in addition to hemorrhage were enlargement of the spleen, liver, lymph nodes, kidney and heart. These are tabulated below.

Enlargement Found at Autopsy (21 cases)

Spleen	19
Liver	18
Lymph nodes	18
Kidney	12
Heart	7

Hemorrhage found at Autopsy (21 cases)

Gastrointestinal	13 (4 massive)
Heart	12
Kidney	12 (1 massive)
Brain	6
Lung	6
Bladder	2

Microscopic examination revealed leukemic infiltration to occur most often in the liver, lymph nodes, kidney, and lung in that order. Less regularly involved were the heart, intestine, pancreas, adrenals, brain, and thymus.

Immediate Cause of Death (21 cases)

Hemorrhage	14
Anemia	6
Congestive heart failure	1
Total	21

The duration of the disease is known in 63 cases. Fifty-two were acute leukemia (lived less than 6 months). The average duration in this group was 2.9 months. Ten cases were subacute leukemia (lived from 6 months to 1 year after the onset). The average duration of this group was 8.5 months. One child lived 15 months and was the only one classified as chronic leukemia (myeloid).

Duration of disease in months (63 cases)

Age in years	Male	Female
0– 1	1¼, 1½, 1	2, 1, 1
1– 2	3¼, ½	8, 2
2– 3	8½, 5¾, 5, 4¾, 3¼, 3, 2¼, ¾, ¼	
3– 4	5, 3, 2¼, 2, 1½, 1½, ½	7¼, 4¼, 3, 2½, 1½, 1¼, 1
4– 5	10½, 5½, 4¾, 2¼	1
5– 6	5¼, 3, 2½, 2½, 1	
6– 7	15, 7, 4, 2¾	½
7– 8	4½	7, 1¼, 1¼
8– 9		11
9–10	1	
10–11	2, ¾	6½
11–12	10¾	
12–13	6	

SUMMARY

1. A review is presented of 65 cases of leukemia in children.

2. There were 34 leukemias of undifferentiated type, 21 lymphoid, 9 myeloid, and 1 monocytic leukemia.

3. Only 11 children lived more than 6 months and only 1 child lived over a year (15 months).

4. Seventy-four per cent of the cases occurred during the first six years of life. Sixth-four per cent were males. The ratio of white to colored patients (corrected for the admission rate) was 2.8 to 1. The onset of the disease was more often in the summer months than in the winter months.

5. Acute infections preceded or accompanied the illness in 45% of the series. Sulfonamide medication had no apparent causal relation to the disease.

6. Bone or joint symptoms were present in 32% when admitted and in 17% they were the chief complaint.

7. Liver enlargement was absent in 32% on admission as was splenomegaly in 20%. Significant lymphadenopathy was absent at the onset in 19%. The skin of 32% of the children was yellow tinted with the sclerae being non-icteric. Bleeding manifestations were discovered in 68% of the cases at the time of admission and a heart murmur was present in 43%.

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OSTEOGENESIS IMPERFECTA CONGENITA

Case Report No. 128

Alfred T. DeVito, M.D. T. W. B. 46–9356

A seventeen day old white male was admitted to this hospital because of imperfect bone formation. The mother noticed that "the back of the baby's head was quite soft and the legs were considerably bowed."

The infant had been born at term in a local hospital on September 27, 1946, 17 days before admission, the birth weight being 1848 grams. The mother was apparently a healthy multipara who experienced no illnesses during her pregnancy; labor was induced because of a dry state and a breech presentation. No instruments were employed. At birth there were no apparent neonatal or congenital difficulties, no neonatal convulsions, or jaundice: the child was said to be active and pink in color. The examination at birth apparently revealed no abnormalities.

The infant was started on a formula and no feeding problems were encountered and the vitamin intake was considered adequate. Two days after birth the mother noticed that the back of the baby's head was quite soft and the legs were bowed. No history of vomiting, dyspnea or syncope could be elicited.

There were two siblings who were both living and well. No familial history of osteogenic difficulties could be obtained.

Physical examination at the time of admission revealed a well nourished, poorly developed male infant not appearing acutely ill. The weight was 1800 grams, length 38 cm.; temperature, pulse and respirations were normal. The head was of an elliptical shape with a circumference of 25.6 cm. Failure of closure of the saggital suture with a marked separation of the parietal bones and marked patent fontanels were noted. The occipital bone was very soft as compared to the firm feeling of the parietal bones. No unusual note was demonstrated on percussion of the skull. The tone and turgor of the skin were good with no rashes bbserved. The sclerae were bluish and no strabismus or nystagmus was noted. The examination of the ears revealed normal markings and normal appearance of the drum and canal. The neck appeared to be abnormally short. The circumference of the chest was 28 cm. The respiratory movements were normal and on auscultation and percussion the lungs were clear. Examination of the heart and abdomen was negative. The femurs were very small and palpation along the anterior aspect of the tibiae revealed a roughening and irregularity.

X-ray studies revealed the following: "Examination of the skull by various techniques reveals the failure of calcification of most of the cranial bones indicative of osteomalacia. The fontanels are patent and bulging as are the

suture lines indicative of increased intracranial pressure. There appears to be a prolapse of the cervical spine into the foramen magnum and the spinus process of the C1 and C2 appear to be fractured. The appearance of the skull is that of platybasia. Examination of the skull by Kopetsky technique reveals no additional information. Examination of the long bones of the upper and lower extremities reveals the presence of a fracture of the acromial process which appears to be healing. There are also healing fractures of the left ulna with bowing of the left ulna and radius. There are fractures of the left femur with bilateral congenital dislocation of the hips.

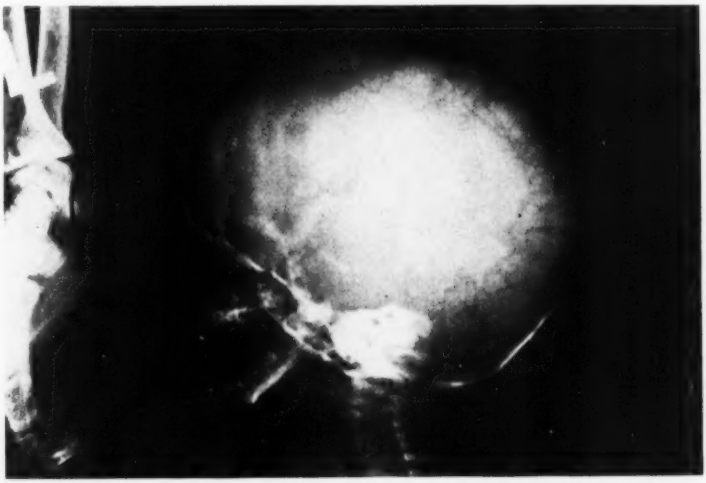

FIG. I. T. W. B. Notice the lacunar appearance with extensive lack of mineralization of the calvarium. Upon palpation the skull felt just like it would appear to feel, like a bag of mush.

Bilateral clubfeet are noted, and anterior bowing of both tibiae and fibulae. Examination of the thoracic and lumbar spine in the apposition reveals no definite evidence of abnormality. Examination of the thoracic cage reveals marked deformity and probably several healed fractures. It is noted that there is marked disturbance of the chondral metaphyses particularly the distal heads of the tibiae and fibulae. *Interpretation:* Generalized osteomalacia, probably indicative of congenital sporadic osteogenesis imperfecta and many of the reported fractures probably occurred in utero."

The infant was retained in the hospital and his course here was uneventful. After 14 days the patient was discharged to a nursing home and after 24 hours succumbed. Reason for death was explained as acute atelectasis.

Pertinent autopsy findings are as follows:

1. Head has an increased occipito-bregmatic diameter as compared with the parietal diameter. The nose is saddle shaped and the sclerae are very

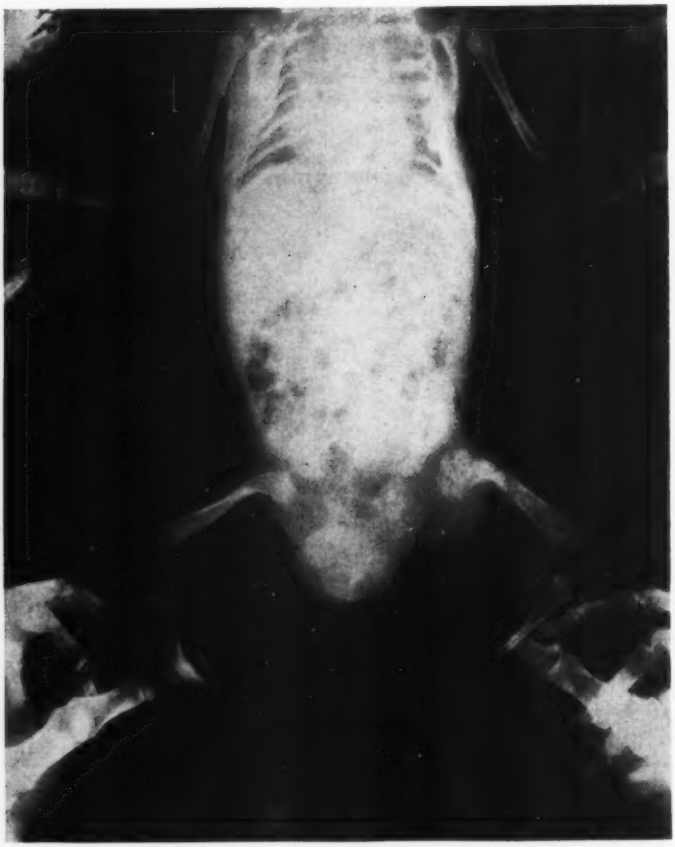

FIG. II. T. W. B. Note the multiple fractures of the left side of the thoracic cage and the proximal head of the left femur with a good deal of demineralization and bowing of the remaining bones consistent with the diagnosis of osteogenesis imperfecta congenita.

blue. The neck is very short; the extremities are short, bowed and irregular.

2. The anterior fontanel measures 5 cm. in its lateral diameter. The

frontal, parietal and parieto-occipital bones are separated by approximately 3 cm.

3. The convolutions of the brain cortex are somewhat flattened.

4. Bone changes: The cartilagenous bones show irregular islands of calcification. This is most marked in the flat ones of the skull. The ribs and the bones of the extremities are very soft. They can be crushed between a thumb and forefinger and feel like corrugated paper. The cut ends of the bones bleed easily. The clavicles and all bones of the extremities are abnormally bowed. Irregularities in the form of excessive callus formation can be palpated along the course of these bones. Viewing the skull from the inside shows a typical platybasia. The diameter of the foramen magnum is about one-half normal.

DISCUSSION

Frederic G. Burke, M.D.: Osteogenesis imperfecta is a general term applied to a condition in which the bones are so fragile that they fracture as a result of slight trauma. There are three clinical types, the first being the congenital in which even intra-uterine movements may occasion fractures, the second, the infantile, in which the characteristics of the disease become evident sometime shortly after birth. A third or late type has been described but probably represents a difference only of degree from the infantile form. According to Caffey[2] this disease is characterized by defective formation of the differentiation of the subperiosteal and endosteal bone. The growth and differentiation of the epiphyseal cartilage are not seriously disturbed. An hereditary background is found in most cases and the severe congenital form of the disease is thought to be recessive in its transmission and the late type is usually dominant. Following fracture, the formation and absorption of callus are normally rapid and in some cases marked deformity results with healing. Blue sclerae are frequently noted in those with the late type but are not often seen in the congenital variety. Otosclerosis and deafness are complications that are not infrequently associated with this disease.

The roentgenologic diagnosis of the congenital variety is not difficult because of the frequency of which multiple fractures, even of the ribs, are found. Differential diagnosis of the infantile form before spontaneous fractures occur offers some difficulty in differentiating from simple disuse atrophy. As in the long bones, the characteristic finding in the vertebrae is a generalized osteoporosis due to defective cortex and spongiosa. In severe cases the weak osteoporotic bodies exhibit compression deformities near their centers with expansion of the nuclei pulposi and spinal curvatures are common. The entire skeleton is usually so poor in lime salts that it is usually hard to obtain good roentgenograms. The skull bones may be so

poorly mineralized as to practically cast no shadow and may appear no more than a fibrous bag evidencing only an occasional spicule of bone. The calvarium is flattened and spinal column may herniate into the region of the foramen magnum.

The case presented presents the classical features of the congenital variety exhibiting all the manifestations of a case of such severity that it was probably incompatible with life. Since this variety is thought to be recessive the chances of its appearing again in this family are rather slim. However, as a recessive factor, it probably will re-appear in subsequent generations.

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RESISTANT URINARY TRACT INFECTION FOLLOWING NEONATAL DIARRHEA

Case Report No. 129

Allan B. Coleman, M.D. S. H. 47–12897

S. H., a four day old negro girl, was admitted to Children's Hospital on December 9, 1947 because of vomiting and diarrhea for 12 hours. She had been born at term at a local hospital of an uncomplicated second pregnancy. Labor and delivery were uneventful, and the birth weight was 6 pounds 9 ounces (2,960 gm.). She nursed vigorously at the breast; her mother's milk "came in" on the third postpartum day, at which time the mother and baby left the hospital.

One sibling, aged 22 months, was in good health. The parents were well and the mother had received adequate prenatal care.

Physical examination on admission revealed a small newborn showing evidence of dehydration. The abdomen was distended and tympanitic. No other abnormalities were noted.

During the 53 day hospital stay the course was afebrile. Treatment consisted of parenteral fluids, blood transfusions, and graduated low caloric feedings. Streptomycin was administered orally (as part of a study in progress) in dosage of 200 mg. every four hours, for seven days. The diarrhea responded very slowly, persisting until the 22nd hospital day. Stool cultures were repeatedly positive for a variety of organisms of doubtful pathogenicity, *Pseudomonas aeruginosa* predominating (see Table I).

The urine showed moderate to heavy content of clumped white cells and granular casts and *Ps. aeruginosa* on culture. Sulfadiazine was administered by mouth for a week with considerable improvement in the urine picture, but prompt exacerbation after it was discontinued. An intravenous pyelogram showed no abnormality. However, the patient was doing well, gaining weight, and was discharged to be followed in the out-patient department.

She was seen regularly, and readmitted to the hospital on March 5, 1948 at the age of three months because of poor appetite, vomiting and failure to gain weight.

Examination on admission revealed a normal temperature, retarded growth, and an ammonia dermatitis of the perineum. The urine contained a small amount of albumin, and many pus cells in clumps. Culture revealed *Ps. aeruginosa*, 25 colonies per cubic centimeter, with a high streptomycin resistance *in vitro* (see Table).

The urine was rendered alkaline by administration of sodium bicarbonate,

TABLE I

Urine and Stool Cultures

DATE	URINE	STOOL
	1st Adm.	
12/9/47		*Proteus vulgaris* *E. coli*
12/20/47		*A. aerogenes* *E. coli* *P. vulgaris* *Ps. aeruginosa*
12/27/47 and 12/28/47		*E. coli* *Ps. aeruginosa*
12/30/47		*E. coli*
1/ 2/48		*Ps. aeruginosa*
1/ 5/48		*E. coli* *Ps. aeruginosa*
3/12/48	*Ps. aeruginosa*	
1/26/48	*Staphylococcus albus* (contaminant?)	
	2nd Adm.	
3/ 5/48	25 colonies/cc.—*Ps. aeruginosa*, resistant to 150 μ/cc. streptomycin 7 colonies/cc.—*Staph. aureus*, resistant to 10 μ/cc. penicillin	
3/13/48		*Ps. aeruginosa* *E. coli* *Staph. aureus*
3/18/48	*Ps. aeruginosa*, resistant to more than 400 μ/cc. Streptomycin	
3/23/48	*Ps. aeruginosa*	
4/ 8/48	*Ps. aeruginosa*	

and streptomycin was administered intramuscularly in dosage of 900 mg. per day for nine days without effect on the urinary findings, and with increase in the streptomycin resistance of the organism (see Table). An intravenous pyelogram again failed to reveal any urinary tract anomaly; a rectal culture was positive for *Ps. aeruginosa*. Streptomycin was therefore discontinued.

The urine was acidified by administration of ammonium chloride and a course of calcium mandelate (0.45 gm. per day in divided doses) was begun. Until this time there had been an irregular, low-grade fever. During the next week, however, the temperature became normal and the urine free of pus, and the patient gained 1½ pounds (682 gm.). Although *Ps. aeruginosa* could still be recovered from the urine, she seemed well and was discharged again to the outpatient department. When last seen a month later, she had gained an additional 2 pounds (910 gm.) and appeared healthy and active.

DISCUSSION

It is a matter of conjecture whether this patient's urinary infection was ascending or hematogenous in origin. In either event, it was almost undoubtedly associated with the presence of *Pseudomonas aeruginosa* in the bowel during the prolonged diarrheal episode.

The absence of a demonstrable urinary tract anomaly leads to the conclusion that the persistent feature of this infection was due to the causative organism. It is probably illogical to blame the streptomycin resistance of this strain on the previous oral administration of the antibiotic, for *Ps. airuginosa* is deservedly notorious for its resistance to therapy.

Our experience with streptomycin in this patient is in accord with that of Pulaski and Seely[1] who reported, in patients with urinary infection caused by gram negative bacilli, 34% cured, 21% improved but without bacteriologic cure, and 45% failures. In the poorly responding groups, the majority showed *Streptococcus faecalis* or *Pseudomonas aeruginosa* culturally. Second courses of streptomycin were of no avail. They concluded that organisms showing an initial streptomycin resistance of 16 micrograms per cubic centimeter, or greater, were not likely to respond to the drug, despit concentrations of better than 1000 micrograms per cubic centimeter of urine.

Therapy of urinary infections has included[2] alkalinization or acidification of the urine, fluid forcing, ketogenic diet, a variety of "urinary antiseptics" of which hexylresorcinol, methenamine, and the dyes are the more prominent, mandelic acid and its salts, sulfonamides and the antibiotics. The multitude of remedies alone suggests the often encountered resistance to therapy.

After failure of streptomycin and sulfadiazine, our patient showed clinical remission after mandelic acid therapy, despite lack of bacteriologic cure. There has been no recurrence to the date of this writing.

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ALKALIGENES FECALIS BACTEREMIA AND MENINGITIS*

Report of Two Cases in Newborn Infants

Case Report No. 130

Harold W. Bischoff, M.D., Adrian Recinos, Jr., M.D., William S. Anderson, M.D., and E. Clarence Rice, M.D.

In reviewing the literature, one is impressed by the variety of organisms which have caused meningitis. Some of these are considered to be harmless nonpathogens, while others are known to be potentially invasive. Many cases of meningitis are reported in the literature which are due to gram-positive or negative bacteria. Some are caused by viral agents, a few claim their etiology in yeasts and molds, and still fewer are caused by metazoan parasites (e.g., Cysticercus).

A review of the literature reveals that, to date, only six cases of meningitis due to organisms of the genus *Alkaligenes* have been reported. The first case caused by an organism of this genus was reported by Gatewood[1] in 1931. In 1934, Mason[2] successfully treated a 12 year old child with *A. fecalis* meningitis by repeated cisternal punctures. In the same year Spray and Hawk[3] reported the disease following otitis media. Kutscher[4] in 1937 reported on a similar case caused by *A. bookeri* and reviewed the literature on gram-negative *Bacillus meningitides*. In 1942 Voorhies and Wilen[5] reported their case of *A. fecalis* bacteremia and meningitis. The most recent report of a case of this sort, occurring in a 42 year old seaman, was made by Terry, McBane and Dean[6] in 1947.

The following two cases of *A. fecalis* bacteremia and meningitis are believed to be the first reported in newborn infants.

Both of these children were born in the same hospital and were transferred to the Children's Hospital when it became evident that their respective illnesses were of a grave nature. One of these children was negro, the other white. They were delivered in different delivery rooms by different doctors, and taken care of in separate nurseries by different nursing staffs.

No definite epidemiologic chain was ever established between the two cases, even though the children were born in the same hospital within two days of each other.

CASE REPORTS

Case #1: B. B. W., a 4 day old white male infant, was delivered after a prolonged second stage of labor (three hours) requiring forceps. No other

* This report appeared in the May 1948 issue of the Journal of Pediatrics and is reprinted with the permission of the editor, Dr. Borden Veeder.

maternal history was available. The birth weight was 6 pounds, 4 ounces (2,840 gm.). Persistent mild cyanosis and crying were noted after birth. Fever appeared on the second day of life, and persisted and reached a peak of 102°F on the fourth and last day. The baby became jaundiced on the third day of life. The following day his condition was so poor that he was given clyses and penicillin. When there was no apparent improvement he was transferred to the Children's Hospital, where he was found to be jaundiced and cyanotic. He did not cry. Respirations were irregular with changes in the breath sounds. A full fontanel was noted. The infant expired during a plasma infusion within an hour after his arrival. Laboratory work on the last day of life revealed hemoglobin 15.0 gm., erythrocytes 4.6 million, leucocytes 12,500, neutrophiles 53 per cent, lymphocytes 43 per cent, and monocytes 4 per cent. Urinalysis was positive for albumin and sugar. The specimen was loaded with clumped leucocytes and granular and hyaline casts.

Necropsy Findings: The body was that of a fairly well developed and nourished white male infant. The cord stump and tie were still attached. The stump was black but not grossly infected. Five cubic centimeters of xanthochromic fluid was obtained by cisternal tap. Examination of this fluid revealed: 750 leucocytes per cubic millimeter with 78 per cent polymorphonuclear leucocytes and 22 per cent lymphocytes; approximately 800 mg. per cent protein; and less than 20 mg. per cent sugar. Gram-negative bacilli were seen on direct smear.

The superficial vessels of the brain were congested, but there was no gross hemorrhage. Scattered over the surface of the brain and particularly between the gyri and along the superficial blood vessels there was a thin whitish and yellowish exudate which was most prominent over the cortex and least over the base. The ventricles contained no hemorrhage or exudate.

Anatomically the remainder of the post-mortem revealed nothing significant. A circumcision had not been performed. There were small quantities of fluid in both pleural cavities and in the peritoneal cavity. The organisms present in spinal fluid ante mortem and in the post-mortem specimens of cisternal fluid, heart blood, urine, splenic fluid, and pericardial fluid, all gave the reactions shown in Table I.

Case #2: B. B. H., a 6 day old negro male infant, was delivered at term without difficulty. No additional maternal history was available. A circumcision was done on the fourth day of life. The following day the infant had a temperature of 102°F. On the sixth day of life his condition became critical, and he was noted to have a temperature of 104°F, convulsions, cyanosis, nuchal rigidity, and a bulging fontanel. He was started on penicillin intramuscularly. Later in the day he was transferred to the Children's Hospital.

Spinal puncture on admission was productive of xanthochromic to bloody fluid containing 1,400 leucocytes (27 per cent polymorphonuclear leucocytes, 65 per cent lymphocytes, and 8 per cent endothelial cells), and 600 mg. per cent protein. The baby was given intramuscular and intracisternal penicillin and oral and subcutaneous sulfadiazine.

In spite of all therapeutic and supportive therapy the child pursued a downhill course and died fifteen hours after admission.

Necropsy Findings: The body was that of a poorly nourished and developed, light-skinned, negro male infant. The umbilical stump was still attached, was firm and black and free of gross infection. The glans penis was

TABLE I

GRAM STAIN	MOTILITY	LIQUEFY GELATIN	INDOLE	VOGES-PROSKAUER	METHYL RED	DEXTROSE	SUCROSE	LACTOSE	MALTOSE	MANNITE	LITMUS MILK
−	+	−	−	−	−	−	−	−	−	−	Sl.alk.*
	Conclusions: *A. fecalis*										

* Sl.alk.—slowly became alkaline.

TABLE II

GRAM STAIN	MOTILITY	LIQUEFY GELATIN	INDOLE	VOGES-PROSKAUER	METHYL RED	DEXTROSE	SUCROSE	LACTOSE	MALTOSE	MANNITE	LITMUS MILK
−	+	−	−	−	−	−	−	−	−	−	Sl.alk.*
	Conclusion: *A. fecalis*										

* Sl.alk.—slowly became alkaline.

swollen, dark red in color, and appeared to be gangrenous. There was no evidence, however, of any direct spread of infection from the penis into the abdominal cavity.

Bloody fluid was withdrawn from the cisterna magna. A direct smear of this fluid revealed the presence of gram-negative bacilli.

The meningeal and pial vessels of the brain were engorged. There was a fresh hemorrhage in the intratentorial region, more marked on the right. Covering the surface of the brain, most marked over the convex surface and between the gyri, was a light yellow-green exudate. The ventricular system and the choroid plexuses were normal. A small blood clot was observed in the fourth ventricle.

The lungs were heavy but crepitant and floated in water. Frothy clear fluid could be expressed by pressure on the lung parenchyma. The pericardial sac contained 10 cc. of dark yellow fluid. The epicardial surface, especially over the auricles, and the great vessels were speckled with a yellowish exudate.

The peritoneal cavity contained 30 to 40 cc. of dark yellow fluid. Filmy adhesions were present between the visceral peritoneum and the anterior abdominal wall. A light yellowish exudate was present, scattered over the intestines and the spleen. The organisms present in the cisternal fluid, pleural fluid, peritoneal fluid, heart blood, and urine, all gave similar reactions, as seen in Table II.

DISCUSSION

According to Topley and Wilson[7], *A. fecalis*, originally named *Bacterium fecalis alkaligenes*, was isolated from human feces by Petrushky in 1896. Although usually a harmless saprophyte in the intestinal tract of man, this organism may occasionally give rise to infections of the enteric type. Mason[2] quotes other authors as describing the general picture of typhoid fever being caused by *A. fecalis*.

The organisms present in the various fluids collected from these two children were identified according to Bergey's Manual[8]. There was complete agreement of bacteriologic evidence in all instances. The results of these bacteriologic determinations have been summarized in Tables I and II.

SUMMARY

Two additional cases of bacteremia and meningitis due to *A. fecalis* are added to the literature. This brings the total to eight.

The two cases reported are the first of bacteremia and meningitis caused by *A. fecalis* in the newborn infant.

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CLINICO-PATHOLOGICAL CONFERENCE

Directed by: E. Clarence Rice, M.D.
Assisted by: Harold W. Bischoff, M.D.
Adrian Recinos, Jr., M.D.
By Invitation: John O. Nestor, M.D.

Harold W. Bischoff, M.D.

A two year old white male was admitted to the hospital on February 24 because of vomiting of twenty-four hours' duration and convulsions.

The past history revealed the child to have been a seven month premature infant weighing seven and a half pounds. He did not do well the first week of life but gained satisfactorily thereafter on an evaporated milk formula. At six months, he began having what was interpreted as intermittent tonic convulsions consisting of drawing up his arms and legs and straining without loss of consciousness. These spasms continued for four months. Physical examination when six months old showed frontal bossing and early closure of the fontanelles. Examination of the skull in the anterior-posterior and lateral positions revealed the sutures to be somewhat widened. There was an area of bizarre-shaped shadows in the parietal bone which was thought to represent blood vessels in that area. In the anterior-posterior as well as the lateral positions there was noted an area of increased density in the posterior portion of the parietal bone. The sella turcica was adjudged to be normal and although the sutures were somewhat separated there was no definite evidence of intracranial pressure. The developmental history showed physical retardation, the patient being unable to sit up or stand at the time of admission. The patient had measles at one year. The family history was non-contributory.

About twenty-four hours prior to entry the patient began to vomit and this continued up to the time of admission. On the way to the hospital the child began having what were described as "minor convulsions."

Physical examination on admission revealed a critically ill, dyspneic child with peripheral cyanosis. The temperature was 102°F. The pupils were constricted and did not respond to light. There were frequent oculo-gyral crises. The muscle tone was poor. Other than a marked flaring of the rib margins, the examination of the chest and abdomen was essentially negative. During the examination there were intermittent generalized spasms of rigidity of short duration.

The child received oxygen, coramine, calcium gluconate and sodium luminal; however, in spite of all these measures, he expired two hours after admission.

DISCUSSION

John O. Nestor, M.D.: Convulsions and vomiting are both common in childhood and are frequently caused by the same pathologic condition, especially when they occur together. The causes of both are so numerous and varied that in a discussion such as this one can only mention briefly the main categories to be considered, namely, expanding intracranial lesions, brain injuries, intracranial infections, extracranial infections, intoxications, metabolic or nutritional disorders, congenital defects, and epilepsy.

One wonders if the convulsions described at the age of six months were actually convulsions or something on the order of colic although it would seem to be a little late for colic to begin and long for it to continue. Apparently the convulsions were afebrile for no particular mention is made of fever until admission to the hospital and then the low grade fever could be explained on the basis of acidosis and dehydration due to vomiting. There is no mention of loss of sphincter control during the convulsions or unusual lethargy. We do not have the aid of important laboratory procedures such as blood calcium, sugar and NPN or a spinal fluid examination. However, it is well to remember that tetany is the most common cause of afebrile convulsions under the age of two and that epilepsy is uncommon under that age.

True oculo-gyric crises are considered by Ford to be almost pathognomonic of epidemic encephalitis. One wonders if the ocular phenomenon described is actually a true oculo-gyric crisis.

Although it is possible to have a 7 months' premature weighing $7\frac{1}{2}$ pounds it would be very unusual. We know that full term babies can range from 5 to 11 pounds and still be normal. Since we are not given the details of the first week of life we must assume that one, some, or all of the following were present to indicate that the baby was not doing well—vomiting, failure to take food, excessive loss of weight, fever and cyanosis.

Frontal bossing may be caused by rickets, syphilis, or prolonged severe anemia and early closure of the fontanel may be normal or due to premature synostosis, arrested cerebral development, or Vitamin D poisoning; however, no evidence is present for or against any of these. Widening of the cranial sutures usually results from increased intracranial pressure, most often due to tumors, abscess, hemorrhage, cyst, or hydrocephalus. The area of increased density is probably calcium deposited in an old collection of blood or in a tumor.

Examination of the x-ray reveals a diffuse, homogenous area of increased density in both posterior parietal regions but mostly on the right. On the right the lateral edge of this area of increased density follows exactly the inner edge of the suture line as though it were limited to that area of the

bone by the line. This suggests the probability of an old subdural hematoma in which calcium has been deposited although such deposition is admittedly rare. The fact that the child was retarded in its development fits in very well with the whole picture.

A neoplasm must be considered but there are several facts against that possibility. First of all, there is no evidence of a primary tumor elsewhere in the body which might have metastasized to the brain. A neuroblastoma is about the only abdominal tumor which would metastasize to the brain long before it became palpable in the abdomen although recently we saw presented at a clinical pathological conference a Wilms tumor which did exactly that. Of course it could be a tumor arising from the brain, meninges or skull but there is no cranial nerve involvement which one would reasonably expect. Also an intracranial tumor would not remain limited to that area of one bone by a suture line; it would be more apt to be definitely one sided. Also the calcification would be spotty.

In summary, we have here a child who did poorly after birth, never developed normally, had bouts of afebrile convulsions and finally became acutely ill and died. X-rays showed evidence of increased intracranial pressure and an area of increased density over the posterior of both parietal bones. It would seem that the cause was an expanding intracranial lesion most probably a subdural hematoma.

PATHOLOGICAL DISCUSSION

E. Clarence Rice, M.D.: The body was that of a poorly developed and nourished white male. The teeth were in poor condition, the upper anterior ones being ground down to the gum margins. The lungs were congested and frothy serous fluid was noted in the trachea and bronchi. With the exception of congestion the examination of the thoracic and abdominal viscera disclosed nothing remarkable.

The findings of note were within the skull. There was some separation of the sutures. Between the dura and the pia-arachnoid and extending over the convexity of the cerebral hemispheres was found a pearly white fibrous membrane 2 mm. thick. This was but loosely attached to the pia-arachnoid. The convolutions of the brain were somewhat flattened. Microscopic examination of the brain showed only congestion. The membrane was an organized subdural hematoma which had undergone some calcification.

Pathologic Diagnosis: Organized subdural hematoma, pulmonary edema and congestion, fatty infiltration of the liver, congestion of abdominal viscera.

Discussion: Calcification of subdural hematoma is an uncommon finding.

Subdural hematomas vary in size and appearance depending on the duration of the process. Where there is recent bleeding the membrane is filled with dark brownish bloody fluid which as time goes on becomes gelatinous in appearance and brown in color. That portion of the membrane adjacent to the dura becomes thickened and vascularized. The clot gradually becomes organized oftentimes with the presence of several layers of material. The membrane over the arachnoid is avascular. Bilateral hematomas are not uncommon. There is no doubt that this condition in children is a more frequent finding at necropsy at this hospital than it was ten years ago. Whether this is due to the fact that more patients with this lesion are being brought to the hospital for surgical relief, to a change in obstetric practice or purely to findings as a result of a higher necropsy percentage I do not know.